1: Int J Cancer. 1996 May 3;66(3):315-21. Related Articles, Link

Co-expression of heparin-binding EGF-like growth factor and related peptides in human gastric carcinoma.

Naef M, Yokoyama M, Friess H, Buchler MW, Korc M.

Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of California, Irvine 92717, USA.

Heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF) is a member of the EGF family of polypeptide growth factors, which includes EGF, transforming growth factor alpha(TGF-alpha), amphiregulin (AR) and betacellulin (BTC). To assess the potential role of HB-EGF in human gastric carcinomas, the expression of HB-EGF and EGF receptor (EGF-R) was examined in normal and cancerous gastric tissues and cultured gastric cancer cell lines. By Northern blot analysis, there was a 4.7-fold increase in HB-EGF mRNA levels in human gastric cancers compared with normal gastric tissues. There was a concomitant 3.9-fold increase in EGF-R mRNA levels in these cancers. Immunostaining revealed co-localization in 72% of the cancer cells of HB-EGF and EGF-R. AR and BTC moieties were not evident by Northern blot analysis. However, using PCR, both AR and BTC mRNA species were demonstrated in normal and cancerous gastric tissues. By Northern blot analysis, HB-EGF, TGF-alpha, AR, BTC and EGF-R mRNA moieties were co-expressed in KATO III and NCI-N87 gastric cancer cell lines. Furthermore, HB-EGF, EGF and TGF-alpha enhanced the growth of both cell lines in a dose-dependent manner. Our findings suggest that HB-EGF is relatively abundant in human gastric cancers and that co-expression of the EGF ligand family may lead to excessive activation of EGF-R in this disorder.

PMID: 8621250 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

1: Cancer Chemother Pharmacol. 1998;42(4):273-9.

The benzoquinone ansamycin 17-allylamino-17-demethoxygeldanamycin binds to HSP90 and shares important biologic activities with geldanamycin.

Schulte TW, Neckers LM.

Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-1928, USA. tschulte@helix.nih.gov

PURPOSE: Benzoquinone ansamycins are antibiotics with anticancer potential. First described as tyrosine kinase inhibitors, they are now frequently used to target HSP90 chaperone function. While herbimycin A and geldanamycin (GA) have been widely used in preclinical studies, both drugs are poor candidates for clinical trials owing to their in vivo toxicity and lack of stability. We therefore examined the biologic effects of 17-allylamino-17-demethoxygeldanamycin (17-AG), an ansamycin derivative with lower in vivo toxicity than GA. METHODS: Binding of 17-AG to HSP90 was studied in vitro using a GA-affinity beads competition assay. We analyzed the drug-induced destabilization of p185erbB2, Raf-1 and mutant p53 in SKBR3 breast cancer cells by Western blotting. The antiproliferative activities of 17-AG and GA were compared using the MTT assay. RESULTS: We found that in a similar manner to GA itself, 17-AG bound specifically to HSP90. It also led to degradation of the receptor tyrosine kinase p185erbB2, the serine/threonine kinase Raf-1 and mutant p53. Both GA and 17-AG displayed comparable antiproliferative effects in SKBR3 and MCF7 cells. Even though HSP90 binding by 17-AG was weaker than by GA, 17-AG and GA caused biologic effects in tumor cells at similar doses. CONCLUSION: 17-AG shares the important biologic features of its parent compound GA. Since 17-AG has a better toxicity profile than GA, it is an interesting candidate benzoquinone ansamycin for clinical development.

PMID: 9744771 [PubMed - indexed for MEDLINE]

Oct 2 2003 18:06:2